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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/192,064	11/13/1998	HARTOUN HARTOUNIAN	07333/043001	9320

36183 7590 03/02/2004

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EXAMINER	
KISHORE, GOLLAMUDI S	

ART UNIT	PAPER NUMBER
1615	

DATE MAILED: 03/02/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/192,064	HARTOUNIAN ET AL.	
	Examiner	Art Unit	
	Gollamudi S Kishore, PhD	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 January 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10,12-35,49 and 51-89* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10,12-35,49 and 51-89* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The filing as RCE and change in power of attorney dated 1-13-04 are acknowledged.

Claims included in the prosecution are 1-10, 12-35, 49 and 51-89.

Claim Rejections - 35 U.S.C. ' 103

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. Claims 1-10, 12-35, 49 and 51-89 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kim (cancer Treatment Reports, 1987) or Assil (arch. Ophthalmol. 1987) or Bonetti (Cancer Chemother. Pharmacol., 1994) or Kim (5,723,147), or Sankaram (5,766,627) in view of Lenk (5,48,441).

The above references of Kim, 1987, Assil, 1987, Bonetti 1994 or Kim 147 or Sankaram, 627 all teach basically the same process of preparation of multivesicular liposomes.

The process involves dissolving the amphipathic lipid and the neutral lipid in chloroform and mixing it with an aqueous solution containing sucrose and forming an emulsion (instant step A), mixing this emulsion with an aqueous solution (step b) and removing the organic solvent and thereby forming the multivesicular liposomes (note the experimental sections in the publications and examples in Kim 147 and Sankaram 627).

What are lacking in these references are the teachings of filtration by cross-flow filtration method and making a sterile preparation.

Lenk while disclosing a method for size separation of particles teaches that there are problems associated with various methods previously available for the preparation of liposomes or vesicles of a select size and that by the cross-filtration method (also called as tangential flow filtration method) allows one to select large quantities of liposomes of a homogeneous, defined size distribution from a heterogeneously-sized population (note the abstract, col. 4, line 12 through col. 6, line 49). Lenk also discloses preparations for various modes of administration and sterile solutions (note col. 15, lines 1-19 and examples).

The use of cross-flow filtration step in the method of preparation of multivesicular lipid particles of Kim, Assil, Bonetti or Sankaram would have been obvious to one of ordinary skill in the art since Lenk teaches the advantages of using such a step in the preparation of vesicles or liposomes. It is deemed within the skill of the highly developed

sciences to prepare a sterile preparation. It is also within the skill of the art to realize that if any composition is given by a systemic route, in the form of an injection in particular, that the preparation should be sterilized. Furthermore, it is clearly evident from Lenk that sterile preparations have to be used if they are administered to mammals. The criticality of the type of mixers and various method parameters recited in instant claims is not readily apparent to the examiner. In the absence of unexpected and unobvious results, these are deemed to be parameters manipulated by an artisan to obtain the best possible results. It is common practice in any field to perform a pilot method and extend it to a large-scale production.

Applicant's arguments have been fully considered, but are not found to be persuasive. Most of applicant's arguments have been addressed before by the examiner (please see prior actions). Applicant once again argues that present claims recite sterilization of the liposomes either at the time of formation through use of sterile starting materials, or after cross-flow filtration, prior to filling and thus, none of the references, either alone or in any combination, teach the ability to control and predetermine multivesicular liposome size at the liposome formation step of the production process, thereby eliminating the need for post-formation size sorting. These arguments are not found to be persuasive. First of all, sterilizing the components used in a composition and preparing a composition under aseptic conditions or sterilizing the composition after it is prepared, when the compositions are meant for human administration, is well known in biological sciences; this is meant to avoid microbial contaminations. With regard to controlling the liposome sizes at the liposome formation

step - the examiner points out that it is common knowledge that smaller liposomes will be formed with more mechanical agitation and vice versa. The examiner had already cited in this context, the reference of Kim (5,422,120, already of record), which shows that by varying the mechanical strength or duration of shaking, or homogenization one can prepare larger or small liposomes (see Example 7 on col. 16).

3. Claims 1-10, 12-35, 49 and 51-89 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kim (cancer Treatment Reports, 1987) or Assil (arch. Ophthalmol. 1987) or Bonetti (Cancer Chemother. Pharmacol., 1994) or Kim (5,723,147) or Sankaram (5,766,627) in view of Lenk as set forth above, further in view of Kwasiborski (6,033,708), Fenski (5,837,282), Mehl (5,885,260), Castor (5,776,486), Moynihan (5,589,189) by themselves or in combination.

1 The teachings of Kim, Assil, Bonetti, Sankaram and Lenk have been discussed above.

Kwasiborski (708) and Fenski (282) both teach a method of preparation of sterile liposome dispersion; the method involves filtering through 0.2 micron filters (note the examples and claims of Kwasiborski; col. 11, line 40 et seq.).

Mehl (260) while disclosing sterile liposome preparations teaches that administration to humans requires that the liposomes be pyrogen free and sterile and advocates the use of filters (note col. 3, line 54 et seq.).

Castor teaches the awareness in the art of sterilizing individual components and solutions and the filtration of liposomes (note col. 2, line 37 et seq.).

Moynihan teaches that the best method for terminal sterile filtration is the sequential filtration of a dispersed liposomes (note col. 3, line 33 et seq.).

One of ordinary skill in the art would be motivated to prepare the multivesicular liposomes in a sterile state because the references of Kwasiborski, Fenski, Mehl, Castor and Moynihan each teach methods that involve the production of sterile liposomes and therefore, a similar sterile production of liposomes is to be expected with instant liposomes also.

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant argues that none of these references teach the control of the particle sizes in relation to energy input at the time of liposome formation. These have been addressed above.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gollamudi S Kishore, PhD whose telephone number is (571) 272-0598. The examiner can normally be reached on 6:30 AM- 4 PM, alternate Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman K Page can be reached on (571) 272-0602. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Gollamudi S Kishore, PhD
Primary Examiner
Art Unit 1615

GSK